Claim 20 (amended). A kit comprising at least the following components:

(a) one or more recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof;

(b) a means for detecting anti-MHC antibodies.

New Claims 22-24:

Claim 22. A kit as claimed in claim 20 which further comprises a solid support together with means for attachment of the MHC molecules.

Claim 23. A kit as claimed in claim 20 wherein the means for detecting said anti-MHC antibodies comprises an antibody which binds to the complex formed between said MHC molecules and naturally occurring antibodies to said molecules.

Claim 24. A kit as claimed in claim 22, wherein said solid support is a spherical bead.

REMARKS

The amendments to claims 1, 4, 17 and 20 are made to clarify the language of the claims. No new matter is introduced by these amendments. Support for new claims 22 and 23 can be found in original claim 20 and support for new claim 24 can be found in original claim 21.

Claims 18, 19 and 21 have been canceled without prejudice from the application. Applicants specifically reserve the right to file a divisional application directed to the subject matter of these claims. Claims 1-17, 20 and 22-24 are pending.

The objection to the drawings referenced the informal drawings filed with the application on March 16, 2001. The bases for objecting to the formal drawings were

clearly these original drawings and not the formal drawings subsequently filed. For the convenience of the Patent Office, we are including a copy of the formal drawings filed on June 21, 2001.

In the outstanding Office Action, the specification was objected to on the basis that it lacks a section entitled "Brief Description of the Drawings." Applicants submit that this objection has been obviated by the amendments above to the specification.

Claims 1-17 and 20 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, claim 1 was rejected on the basis that the claim insinuates that a binding event has occurred, but does not recite a step in which a binding event has occurred. The claim also was rejected on the basis that there was insufficient support for "the binding" in line 7 and that "functionally equivalent variants" was vague. Applicants respectfully submit that the basis for the first two of these rejections have been obviated by the amendments set forth above to claim 1. With regard to the examiner's concern regarding the recitation of "functionally equivalent variants," Applicants have amended this term to clarify that the variants also are recombinant. Applicants also submit that the examiner's assertions that the term is not defined in the specification, these entities are described in detail in the application, particularly on pages 9 and 10 of the specification as filed. Applicants thus respectfully submit that these terms are well supported by the description of the invention in the application.

The examiner rejected claim 4 on the basis that there was insufficient basis for the recitation of "the heavy chain." The claim has been amended to provide

antecedent basis for that term. In claim 17, the word "via" was objected to. That word has been replaced in the amendment to claim 17 above. finally, in claim 20, the phrases beginning with "optionally" and "preferably" were objected to. Both of these phrases have been deleted, and the subject matter of those phrases has been reintroduced in two new claims.

Claims 1-3, 5, 9-11, 13, 16 and 17 have been rejected under 35 U.S.C. § 102(a) as anticipated by an abstract the examiner identified as Ogg et al. (In fact, the first-named author on the abstract is A.W. Harmer.) The examiner asserted that this reference discloses the use of recombinant biotinylated HLA molecules bound onto streptavidin microspheres, contacting these molecules with a serum sample, and detecting the binding of anti-HLA to the HLA molecules. The reference also was said to disclose the use of FITC-conjugated anti-IgG antibody and flow cytometric analysis. As shown below, this reference properly cannot be cited against the claims of this application under §102(a).

The abstract by Harmer et al. was published from the British Transplantation 2nd Annual Congress, March 29-31, 1999. The present application was filed less than one year later, on March 17, 2000. The abstract lists five authors, four of whom (i.e., all but G.S. Ogg) are named as inventors on the present application. Submitted herewith is a declaration by co-inventor Michael Bunce, which explains that Graham Ogg properly was not named as an inventor on the application Graham Ogg was listed as an author on the abstract as he made available materials to the inventors materials that they did not have in their possession. As the inventors' work could not have proceeded

without his help, he was listed as a co-author on the abstract, but he did not contribute to the conception or reduction to practice of the invention described and claimed in the present application. Inasmuch as the work described in the publication is by the named inventors and was published less than one year prior to the filing date of the present application, the abstract is not properly a reference under 35 U.S.C. §102(a).

Claims 4 and 6-8 have been rejected under 35 U.S.C. §103(a) as obvious over Ogg et al. cited above in view of Tan et al. The examiner asserted that the subject matter of the claims differs from that of the Ogg et al. abstract in that the latter does not teach the use of a recombinant heavy chain. The examiner asserted, however, that Tan et al. disclose recombinant HLA heavy chain molecules and that it is advantageous to use such molecules for improved economy and efficiency and that it thus would have been obvious to incorporated recombinant HLA heavy chain molecules as taught by Tan et al. into the method of Ogg et al. This rejection is traversed.

As Applicants have shown, the reference by Ogg et al. (Hamer et al.) is not properly citable against the claims of this application. As the secondary reference taken on its own certainly does not teach or suggest the claimed invention, Applicants respectfully submit that this rejection should be withdrawn.

Claim 12 has been rejected under 35 U.S.C. §103(a) as obvious over Ogg et al. in view of U.S. Patent 5,292,641, issued to Pouletty et al. The examiner asserted that Ogg et al. differs from the claimed invention in failing to teach that the solid support can be nitrocellulose, but that the secondary reference discloses the immobilization of HLA antigens on a nitrocellulose support. This rejection is traversed.

Again, as shown above, the reference by Ogg et al. (Hamer et al.) is not properly citable against the claims of this application. As the secondary reference taken on its own certainly does not teach or suggest the claimed invention, Applicants respectfully submit that this rejection should be withdrawn.

Claims 14 and 15 were rejected under 35 U.S.C. §103(a) as obvious over the Ogg et al. abstract in view of U.S. Patent 6,218,363, issued to Baserga et al. The examiner asserted that Ogg et al. differ from the claimed invention in that the abstract fails to disclose that the recombinant HLA is synthesized in a prokaryotic expression system. He asserted that Baserga et al. disclose that MHC or HLA Class I molecules can be produced by recombinant DNA techniques and that it would have been obvious to synthesize the recombinant HLA as taught by Baserga et al. for the method of Ogg et al. because Baserga et al. show that these recombinant molecules retain the therapeutic or diagnostic activity of the naturally occurring molecule and provide methods of identifying MHC Class I peptides. This rejection is traversed.

As in the previous rejections in which the examiner relied upon the abstract by Ogg et al., that reference is not properly citable against the claims of this application. As the secondary reference taken on its own certainly does not teach or suggest the claimed invention, Applicants respectfully submit that this rejection should be withdrawn.

Claim 20 was rejected under 35 U.S.C. §103(a) as obvious over Ogg et al in view of Pouletty et al. and further in view of U.S. Patent 5,420,016, issued to Boguslaski et al. The examiner asserted that the primary and secondary references differ from the

claimed invention in that they fail to teach the packaging of the components into a kit, but that this deficiency is compensated by the tertiary reference, which does teach assembling various system components into a test kit. He asserted that it would have been obvious to assemble the various components of the modified method of Ogg et al, into kits as taught by Boguslaski, because Boguslaski shows that test kits are more convenient for the test operator. This rejection is traversed.

Again, the teachings of the primary reference properly are not available as a reference against the subject matter of the claims of the present application. The secondary and tertiary references, taken independently or in combination, do not suggest the present invention. Accordingly, this rejection should be withdrawn.

Claims 1-3, 9-11 and 14-17 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent 5,948,627, issued to Lee et al. in view of U.S. Patent 6,218,363, issued to Baserga et al. The '627 patent was described as disclosing a method for detecting HLA antibodies through a method involving adding serum from a patient to microbeads containing HLA antigens and incubating the serum and microbeads for sufficient time for anti-HLA antibodies to bind to the HLA antigens. The Patent also was said to disclose the addition of a labeled ligand capable of specifically binding with anti-HLA antibodies bound to the HLA antigens and detecting the presence of labeled ligand bound to those antigens. The examiner acknowledged that the '627 Patent fails to teach the use of recombinant MHC or HLA molecules.

The secondary reference was described as disclosing modified MHC or HLA Class I molecules that are useful as an antigens for the detection of antibodies

thereagainst and as disclosing that MHC or HLA Class I molecules can be produced by recombinant DNA techniques. The '363 Patent further was said to disclose that recombinant MHC or HLA Class I molecules are produced in the host by expression. The examiner found that it would have been obvious to substitute the recombinant MHC or HLA Class I molecules as taught by the '363 patent for those of the '627 Patent because the formed discloses that modified MHC or HLA molecules provide for a method of detecting antibodies against these molecules. This rejection is traversed.

The '363 patent describes natural or mutant HLA or MHC peptides which can be used for killing cancerous cells *in vivo* or for generating agonistic or antagonistic interactions to that toxic effect. The invention as defined by this patent extends to any peptide that retains a therapeutic or diagnostic ability, including those made by recombinant techniques. The patent is not concerned with MHC molecules or their mutants or even with peptides of such molecules. Rather, it focuses on peptides which bind in MHC molecules (see, for example, column 6, lines 14-16) to form the final complex. They are short in length (column 6, line 8 and column 8, line 62).

Thus, these are peptides *per se* which have been found to be useful as toxic agents for treating cancer by a method independent of the immune system (column 3, line 9) and rather non-specifically (column 3, lines 13-17). As such, this tells the reader nothing more than that some small peptides (which are not derived from the MHC molecule), which can by synthetically produced as toxic to cancer cells and that mutants of these peptides retain their function of toxicity, which is perhaps not surprising as it is expected the peptide would not display a folded conformation. The

reference says nothing about recombinant MHC molecules and whether such molecules would retain their function or tertiary structural properties, such as antibody binding.

Thus, a combination of the two cited references is incompatible and at best would lead to the use of recombinant peptides in complex with naturally occurring MHC molecules. There clearly is no motivation in the '627 patent to make such molecules and so also no motivation to combine the teachings of the '363 patent with those of the '627 Patent.

Prior to the present invention, the prior art relied exclusively on the use of naturally isolated MHC or HLA molecules for methods MHC or HLA antibody detection. No prior art of which Applicants are aware used recombinant MHC or HLA molecules for detecting anti-MHC antibodies or anti-HLA antibodies, respectively. Although recombinant MHC/HLA molecules have been generated previously, they have been used only in T-cell assays. T cells utilize a different epitope on the MHC or HLA molecules in comparison to antibodies, and T-cell binding is very dependent on the peptides loaded into the groove of the MHC or HLA molecule. The T-cell receptor of a particular cell is absolutely specific for a unique peptide/MHC or unique peptide/HLA combination. Thus, recombinant molecules which present that peptide are compatible with T-cell assays. In contrast, MHC/HLA antibodies are not directed to the peptide and bind to the MHC/HLA molecule itself. Thus, only molecules retaining absolute epitopic integrity could be used and it was assumed that this could be found only in naturally occurring molecules. In particular, it was assumed that the peptide presented in the

groove of the MHC/HLA molecule, which could alter the conformation of the MHC/HLA molecule, would affect epitopic integrity. The Applicants, however, investigated this and surprisingly found that the peptide bound in the MHC/HLA groove is irrelevant during antibody binding. As a consequence, despite the previous expectations, recombinant MHC/HLA molecules can be used in these methods.

Furthermore, naturally occurring MHC and HLA molecules are heavily glycosylated. The recombinant molecules of the invention can be synthesized in prokaryotic systems, which does not allow for glycosylation of the protein. Lack of glycosylation of recombinant peptides has been known to alter the conformation of the recombinant protein and alter the ability of antibodies to bind to the protein. As each MHC or HLA molecule has unique glycosylation sites, the position and amount of glycosylation can vary. The Applicants surprisingly discovered that the MHC and HLA molecules can be synthesized recombinantly in prokaryotic systems, lack glycosylation, and still provide an epitope for antibody binding. The Applicants thus have developed technology which went against the current thinking in their field at the time. The conventional wisdom is evident in such references as that by Lee et al., which makes absolutely no reference to using synthetic molecules. As such, the use of recombinant molecules in the methods of the present invention clearly are inventive, and Applicants request that the rejection be withdrawn.

In view of the foregoing amendments and discussion, Applicants respectfully submit that the pending claims are in condition for allowance.

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Marked up copy of amended claims:

Claim 1 (amended). A method of detecting the presence of anti-MHC antibodies in a sample comprising contacting said sample with one or more recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof which each bind to a specific MHC antibody, if present in said sample, and detecting the binding or absence of binding of said antibodies to said recombinant MHC molecules, variants, derivatives or fragments thereof.

Claim 4 (amended). The method as claimed in claim 3, wherein said recombinant MHC or HLA molecule comprises a heavy chain and wherein the heavy chain of said MHC or HLA molecule is recombinant.

Claim 17 (amended). The method as defined in claim 1 or claim 2 wherein the bound antibody is detected ~~via~~ by an immunosorbent assay using an antibody conjugated to a signaling means.

Claim 20 (amended). A kit ~~comrising~~ comprising at least the following components:

(a) one or more recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof;

~~(b) optionally a solid support, together with means for attachment of the MHC molecules and~~

~~(c)~~ (b) a means for detecting anti-MHC antibodies. ~~preferably an antibody which binds to the complex formed between said MHC molecules and naturally occurring antibodies to said molecules~~.